Supplementary materials

Development of an adverse drug reaction network to predict drug toxicity

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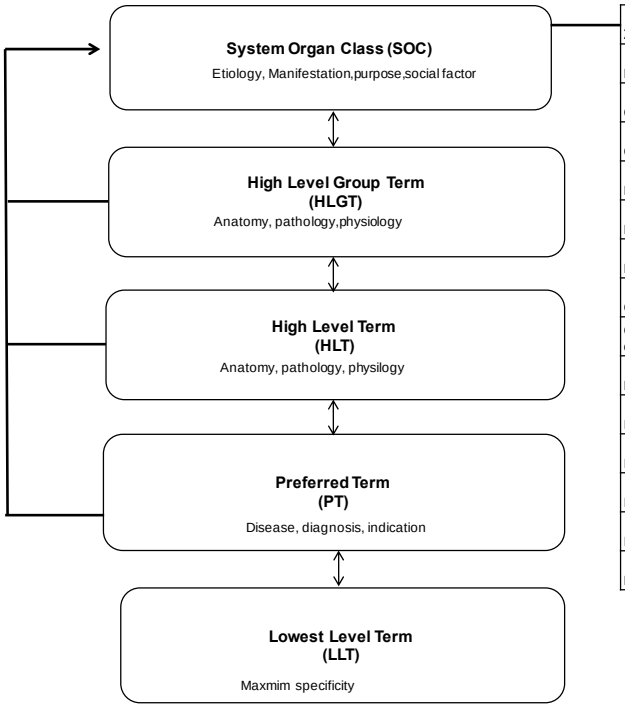

27 System Organ Class (SOC)	
Blood and lymphatic system disorders	Musculoskeletal and connective tissue disorders
Cardiac disorders	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Congenital, familial and genetic disorders	Nervous system disorders
Ear and labyrinth disorders	Pregnancy, puerperium and perinatal conditions
Endocrine disorders	Product issues
Eye disorders	Psychiatric disorders
Gastrointestinal disorders	Renal and urinary disorders
General disorders and administration site conditions	Reproductive system and breast disorders
Hepatobiliary disorders	Respiratory, thoracic and mediastinal disorders
Immune system disorders	Skin and subcutaneous tissue disorders
Infections and infestations	Social circumstances
Injury, poisoning and procedural complications	Surgical and medical procedures
Investigations	Vascular disorders
Metabolism and nutrition disorders	

Fig S1: The hierarchical structure of MedDRA and the list of 27 SOC. The structure of element of MedDRA was a five-tiered hierarchy of terms. Each term provided the different requirement of specificity. Lowest Level Term (LLT) had the maximum specificity. Every subordinate level was linked to more than one superordinate term (For example: LLT were subordinate to PT which means one LLT was linked to more than one PT). System Organ Class (SOC) that was the highest level in MedDRA terminology. Due to its multi-axiality characteristic, it allowed a term to be represented in more than one SOC, except LLT.

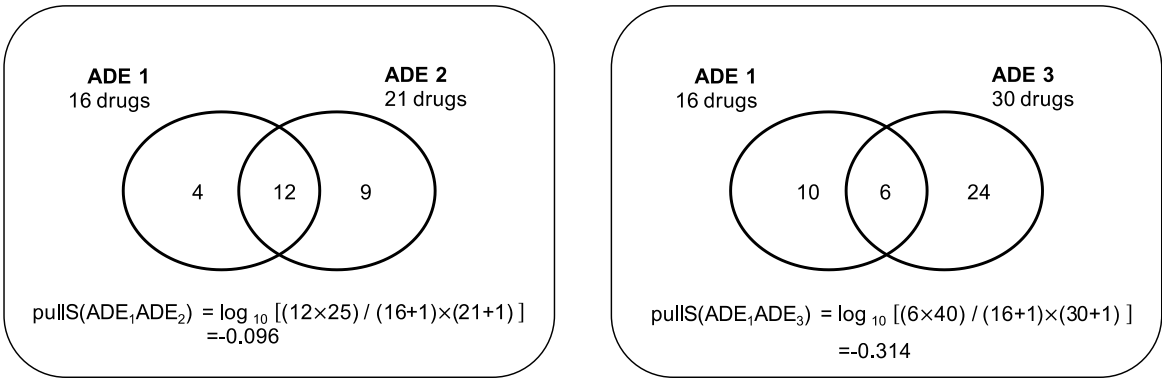

Figure S2: Examples of the pull-down score (pullS). PullS were calculated between each pair of ADE in order to prioritize uncharacterized ADEs that are more likely to occur for a drug, using as input its known ADEs. The Venn-diagrams show two examples involving three ADEs. The values represent the number of drugs connected to either ADE1, ADE2, ADE3. The pullS for ADE1-ADE2 and for ADE1-ADE3 are calculated as shown. In this example, the pullS indicates that there is more confidence in the association ADE1-ADE2, than in the ADE1-ADE3 association.

Table S1: Identified adverse effects for safinamide. List of the most significant adverse drug effects (ADEs) identified by our approach using the pull-down score system (PullS) and the developed ADE model. In grey, the predicted ADEs for which no literature support was found.

Known ADE	Predicted ADEs	PullS	Reference
Parkinsonism_hyperpyrexia_ syndrome	Sudden_onset_of_sleep	-0,967	[1]
	Compulsive_shopping	-1,028	[1,2]
	Jealous_delusion	-1,030	[3]
	Dopamine_dysregulation_syndrome	-1,032	-
	Compulsive_sexual_behaviour	-1,053	[1,2]
	On_and_off_phenomenon	-1,089	[2]
	Gambling_disorder	-1,097	[1,2]
	Impulse-control_disorder	-1,098	[1,2]
	Hypersexuality	-1,139	[1,2]
	Stereotypy	-1,209	[2–5]
	Impulsive_behaviour	-1,219	[1,2]
	Bradykinesia	-1,226	[2–5]
	Obsessive-compulsive_disorder	-1,226	[1,2]
	Neuroleptic_malignant_syndrome	-1,227	[2,6,7]
	Parkinsonism	-1,227	[2]
	Drug_withdrawal_syndrome	-1,230	[2,6,7]
	Parkinson's_disease	-1,230	[2]
	Muscle_rigidity	-1,230	[2,6,7]
	Delusion	-1,231	[3]
	Psychomotor_hyperactivity	-1,232	[2]

Table S2: ADEs reported in FDA pre-marketing reports for safinamide. All predicted ADEs were considered, independently of the significance of the pull-down score.

Drug	Predicted ADEs indicated in FDA reports	PullS	Reference
Safinamide	Impulsive_behaviour	-1,219	[2]
	Dyskinesia	-1,234	[2]
	Orthostatic_hypotension	-1,236	[2]

	Psychotic_disorder	-1,236	[2]
	Agitation	-1,238	[2]
	Hallucination	-1,238	[2]
	Feeling_abnormal	-1,240	[2]
	Fall	-1,241	[2]
	Nausea	-1,241	[2]
	Insomnia	-1,241	[2]
	Drug_interaction	-1,241	[2]
	Confusional_state	-1,241	[2]

Table S3: Identified adverse effects for sonidegib. List of the most significant adverse drug effects (ADEs) identified by our approach using the pull-down score system (PullS) and the developed ADE model. In grey, the predicted ADEs for which no literature support was found.

Known ADE	Predicted ADEs	PullS	Reference
Febrile_neutropenia	Nicotinic_acid_deficiency	-4,96 e-04	-
	Lower_respiratory_tract_infection_fungal	-0,724	[8]
	Juvenile_melanoma_benign	-0,898	[8]
	Chronic_lymphocytic_leukaemia_recurrent	-0,898	-
	Differentiation_syndrome	-0,966	[9]
	Neutropenia	-1,033	[10]
	Pyrexia	-1,071	[8]
	Thrombocytopenia	-1,072	-
	Focal_nodular_hyperplasia	-1,083	-
	Mucosal_inflammation	-1,092	-
	Sepsis	-1,100	[11]
	Richter's_syndrome	-1,106	-
	Pneumonia	-1,112	[8]
	Disease_progression	-1,123	[12]
	Anaemia	-1,125	-
	Bone_marrow_failure	-1,151	-
	Pancytopenia	-1,157	-
	Diarrhoea	-1,164	[12]
	Platelet_count_decreased	-1,165	-
	Vomiting	-1,167	[12]

Table S4: ADEs reported in FDA pre-marketing reports for sonidegib. All predicted ADEs were considered, independently of the significance of the pull-down score.

Drug	Predicted ADEs indicated in FDA reports	PullS	Reference
Sonidegib	Diarrhoea	-1,164	[12]
	Nausea	-1,174	[12]
	Vomiting	-1,167	[12]
	Decreased_appetite	-1,222	[12]
	Fatigue	-1,234	[12]
	Abdominal_pain	-1,289	[12]
	Weight_decreased	-1,360	[12]
	Headache	-1,389	[12]
	Pain	-1,402	[12]
	Pruritus	-1,474	[12]
	Alopecia	-1,485	[12]
	Myalgia	-1,537	[12]
	Dysgeusia	-1,618	[12]
	Muscle_spasms	-1,700	[12]
	Musculoskeletal_pain	-1,811	[12]
	Foetal death	-2,012	[12]
	Teratogenicity	-2,133	[12]

Table S5: Identified adverse effects for rufinamide. List of the most significant adverse drug effects (ADEs) identified by our approach using the pull-down score system (PullS) and the developed ADE model. In grey, the predicted ADEs for which no literature support was found.

Known ADEs	Predicted ADEs	PullS	Reference
Seizure	Product_tampering	-2,81 e-04	-
	Postictal_psychosis	-0,125	-
	Infantile_spasms	-0,301	[13]
	Drug_dose_titration_not_performed	-0,397	[14]
	Cerebrospinal_fluid_leakage	-0,668	-
	Neuroblastoma	-0,918	[13,15]
	Anomaly_of_external_ear_congenital	-0,951	[16]

	Selective_abortion	-0,951	[13]
	Hyponatraemic_seizure	-0,951	-
	Proctitis	-0,967	-
	Tongue_blistering	-0,973	-
	Vomiting	-0,980	[13]
	Confusional_state	-0,989	[17]
	Hordeolum	-0,997	-
	Toxicity_to_various_agents	-1,001	[13,18]
	Nausea	-1,005	[13]
	Drug_ineffective	-1,012	[19,20]
	Somnolence	-1,019	[13]
	Hypotension	-1,020	[17]
	Drug_interaction	-1,023	[13]
Status_epilepticus	Clonic_convulsion	-1,047	[17]
	Psychogenic_seizure	-1,166	-
	Congenital_intestinal_malformation	-1,243	[13]
	Generalised_tonic-clonic_seizure	-1,352	[13,21]
	Seizure	-1,359	[13,21]
	Myoclonus	-1,367	[13,21]
	Congenital_herpes_simplex_infection	-1,369	[13,22]
	Dyskinesia	-1,373	[23]
	Drug_ineffective	-1,384	[19,20]
	Muscle_contracture	-1,392	[13,21]
	Confusional_state	-1,403	[17]
	Vomiting	-1,415	[13]
	Pyrexia	-1,418	[17]
	Condition_aggravated	-1,422	[13,21]
	Epilepsy	-1,426	[13,21]
	Toxicity_to_various_agents	-1,426	[13,18]
	Depressed_level_of_consciousness	-1,427	[13]
	Drug_interaction	-1,428	[13]
	Tremor	-1,429	[23]
	Coma	-1,432	[17]

Table S6: ADEs reported in FDA pre-marketing reports for rufinamide. All predicted ADEs were considered, independently of the significance of the pull-down score.

Drug	Predicted ADEs indicated in FDA reports	PullS	Reference

Rufinamide	Postictal_psychosis	-0,125	[13]
	Nausea	-1,005	[13]
	Completed_suicide	-1,054	[13]
	Headache	-1,062	[13]
	Dizziness	-1,064	[13]
	Fatigue	-1,097	[13]
	Decreased appetite	-1,105	[13]
	Electrocardiogram_QT_prolonged	-1,112	[13]
	Multiple_organ_dysfunction_syndrome	-1,197	[13]
	Neutropenia	-1,230	[13]
	Leukopenia	-1,267	[13]
	Urinary incontinence	-1,345	[13]
	Somnolence	-1,445	[13]
	Increased appetite	-1,594	[13]
	Thrombocytopenia	-1,612	[13]
	Bundle branch block right	-1,622	[13]
	Atrioventricular block first degree	-1,632	[13]
	Pollakiuria	-1,653	[13]
	Dermatitis allergic	-1,662	[13]
	Nephrolithiasis	-1,679	[13]
	Dysuria	-1,761	[13]
	Lymphadenopathy	-1,782	[13]
	Enuresis	-1,797	[13]
	Polyuria	-2,206	[13]

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